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EXAMINER	
STRZELECKA, TERESA E	

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1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,689	WILLIAMS, JOHN G.K.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *4-17,20,21,24,25 and 27-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,18,19,22,23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/11/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed May 11, 2009. Claims 1-46 were previously pending, with claims 4-17, 20, 21, 24, 25 and 27-46 withdrawn from consideration.

2. Applicant amended claims 1 and 29. Claims 1-3, 18, 19, 22, 23 and 26 will be examined.

3. Applicant's amendments overcame the rejection of claims 1-3, 18, 19 and 26 under 35 U.S.C. 112, second paragraph. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" section below.

4. This office action contains new grounds for rejection (new matter) necessitated by amendment.

Terminal Disclaimer

5. The terminal disclaimer filed on May 11, 2009 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the U.S. Patent No. 7,462,468 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Therefore the obviousness-type double patenting rejection of the instant claims over the claims of the '468 patent is withdrawn.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on May 11, 2009 was filed after the mailing date of the non-final office action on February 11, 2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

7. Applicant's arguments filed May 11, 2009 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 1-3, 18, 19 and 26 under 35 U.S.C. 102(a) as anticipated by Motz et al., Applicant argues that Motz et al. do not anticipate the claims as amended, since "...the anchor in the subject application is *part* of the attachment complex, whereas in Motz *et al.* there exists two distinct components. In addition, as presently claimed, it is the anchor as part of the attachment complex which entraps the DNA and irreversibly associates the polymerase and the nucleic acid. In Motz *et al.,* the second component holds the DNA and cycles off. Further, in the instant claims, although one end of the anchor is attached to the polymerase, the other end of the anchor is attached to 1) the polymerase, ii) a tether or iii) a support. The present anchor has two ends, both of which are attached ("anchored"). In Motz *et al.,* the first component is grafted to the carboxy terminus and presumably becomes the new carboxy terminus. The claimed features are simply not taught by Motz *et al.*"

Applicant argues limitations which are not present in the claims. As explained in the "Claim Interpretation" section below, the claims require a polymerase with an anchor covalently attached to it, and with a second end attached either to the polymerase, or to a topological tether, or to a support, and an attachment complex which comprises the anchor, where the function of the anchor is to entrap the nucleic acid to increase processivity. Therefore the anchor is a part of both the polymerase and the further unspecified attachment complex. Motz et al. teach the following elements: i) Taq polymerase, ii) a PCNA-binding domain (=anchor), covalently attached to the polymerase at its C-terminus, iii) PCNA (=topological tether), which attaches a DNA molecule to the polymerase during replication. Therefore, the "attachment complex" of Motz et al. is the PCNA molecule + PCNA-binding domain, anticipating the claim limitations.

The rejection is maintained.

B) Regarding the rejection of claims 19 and 22 under 35 U.S.C. 103(a) over Motz et al. and Bianco et al., Applicant argues that since Motz et al. do not anticipate claim 1, the rejection should be withdrawn.

Arguments regarding the anticipation of claim 1 by Motz et al. were presented above.

The rejection is maintained.

C) Regarding the rejection of claim 23 under 35 U.S.C. 103(a) over Motz et al. and Williams, Applicant argues that since Motz et al. do not anticipate claim 1, the rejection should be withdrawn.

Arguments regarding the anticipation of claim 1 by Motz et al. were presented above.

The rejection is maintained.

D) Regarding the rejection of claims 1-3, 18, 19, 22, 23 and 26 under 35 U.S.C. 112, first paragraph, written description, Applicant argues the following:

i) "Applicant is not claiming new polymerases, but modifying polymerases to make them new."

ii) None of the case law cases cited in the rejection are on point.

iii) "Applicant is claiming a *polymerase* modified to include "accessories" to have longer read lengths. It does not matter which polymerase is modified, only that its processivity is increased. In the specification at paragraph 57, Applicant states "[a]lthough the polymerase selected for use in this invention is not critical, preferred polymerases are able to tolerate labels on the γ-

phosphate of the NTP. The representative number of species requirement is an issue when there is substantial variation in the genus. This is not an issue when the type of polymerase is not critical."

There are two issues raised by Applicant. The first, that Applicant does not claim any new polymerase, but a polymerase with additional elements added, is not correct. The claims encompass polymerases modified by covalent additions of any number of molecules, including replacement of any part of a polymerase with a different sequence, as evidenced by Motz et al., for example, where the C-terminus of Taq polymerase was replaced by the PCNA-binding domain. Therefore, Applicant does claim a huge genus of new polymerases. The other issue is the representative number of species. Even assuming that a single polymerase is claimed, again, the genus comprises polymerases with replacement of any part of their amino acid sequences with another sequence, polymerases with additional moieties attached, like peptides, nucleic acids, etc. Therefore, the cited case law is very appropriate: Applicant claims a structure solely by its function, without any structure, i.e., amino acid sequence, including the starting sequence of the polymerase. In a genus which has billions of possibilities, Applicant did not show a possession of a single species which is an example of the claimed genus at the time of the invention.

The rejection is maintained.

E) Regarding the rejection of claims 1-3, 18, 19, 22, 23 and 26 under 35 U.S.C. 112, first paragraph, enablement, Applicant argues the following:

i) Regarding working examples and guidance in the specification, Applicant cites a passage from a reference published in Nucleic Acids Research in 2008, describing a polymerase with two peptide biotinylated "legs" which served to attach the polymerase to a substrate. Applicant states

"The foregoing reference unequivocally demonstrates that the claimed invention works. The anchor and attachment complex as claimed *convert a naturally nonprocessive DNA polymerase into a highly processive one capable of incorporating thousands of nucleotides without dissociating from the template.* This reference demonstrates that the claimed invention is fully enabled.

Moreover, the specification shows no fewer than 11 Examples on how to make and use the claimed invention. Under MPEP § 2164.01 (b) as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied."

First, Applicant is reminded that the claims need to be enabled at the time of the invention (see MPEP 2164.01):

"2164.01 Test of Enablement [R-5]

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also *United States v.*

Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). >Any part of the specification can support an enabling disclosure, even a background section that discusses, or even disparages, the subject matter disclosed therein. *Callicrate v. Wadsworth Mfg., Inc.*, 427 F.3d 1361, 77 USPQ2d 1041 (Fed. Cir. 2005) (discussion of problems with a prior art feature does not mean that one of ordinary skill in the art would not know how to make and use this feature).< Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984)." (emphasis added)

At the time of the invention there was one polymerase, that of Motz et al., that had the structure which performed the claimed function. Applicant did not obtain another polymerase until over five years after the earliest priority date of the instant application. As to the 11 examples, they are as follows:

1) **"Example 1. Introduce a unique cysteine on the protein surface for attaching a fluorophore**

A unique cysteine amino acid is placed on the surface of Therminator polymerase to attach the fluorescent probe. This is accomplished by site-directed mutation of the Therminator gene in two steps. First, the single native surface-exposed cysteine, C223, is eliminated by mutation to serine, resulting in the mutant C223S. Mutant C223S has no surface-exposed cysteines. Next, a new cysteine is uniquely placed on the protein surface by constructing the mutant E554C. The new

cysteine is located on the rim of a cleft in the protein, near the location of a quencher on a bound nucleotide. The resulting mutant is C223S:E554C."

The example is purely prophetic.

2) **"Example 2. Add histidine patches to the protein surface attaching anchors**

Two histidine patches are engineered onto the surface of the C223S:E554C Therminator protein by making the multiple mutations D50H:T55H:E189H:R196H:K229H. The resulting mutant, C223S:E554C:D50H:T55H:E189H:R196H:K229, is called "ThioHis"".

Again, a prophetic example.

3) **Example 3. Circularization of target DNA**

Does not deal with polymerase structure.

4) **"Example 4. Protein modifications**

[10107] The ThioHis Therminator mutant protein (Example 2) is conjugated to tetramethylrhodamine-5-maleimide (Molecular Probes) at position C554. Anchors (biotin-X nitrilotriacetic acid, Molecular Probes) are added to bind to the two histidine patches and the modified protein is purified."

Again, a prophetic example

5) **"Example 5. Anchor protein-DNA complexes to glass coverslips**

[0108| The modified ThioHis protein (Example 4) is mixed with the primed circular template DNA (Example 3) to form polymerase-DNA complexes. The complexes are added

to a streptavidin-coated glass coverslip to topologically trap the DNA between the protein and the glass surface. The coverslip is washed prior to sequencing the immobilized DNA."

A prophetic example.

6) **Example 6. Synthesis Of dUTP--y-TMR**

Does not deal with protein modifications.

7) **Example 7. Strep-Tag II T7 DNA Polymerase**

Describes addition of a peptide tag to a 5'-terminus of T7 DNA polymerase modified to be exo-, expression and purification of the protein.

8) **Example 8. Polymerase Immobilization**

Describes immobilization of the polymerase obtained in Example 7 to a glass coverslip and prophetic example of immobilization to nickel nanodots. There is no indication that the peptide tag served as an anchor which entrapped the nucleic acid during amplification and that its presence resulted in increased processivity.

9) **Example 9. Determination Of Cystic Fibrosis Mutant**

Prophetic example of using the polymerase obtained in Example 8 to determine mutations in a cystic fibrosis gene.

10) **Example 10. Microscope Setup**

Does not deal with making the claimed polymerase.

11) **Example 11. Data Acquisition And Analysis**

Does not deal with making the claimed polymerase.

Therefore, none of the 11 examples describes obtaining a claimed polymerase-DNA complex. Paraphrasing Applicant's own words: the specification does not disclose at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims, therefore the enablement requirement of 35 U.S.C. § 112 is not satisfied.

ii) Regarding the issue of unpredictability, Applicant cites a reference of Patel et al., and specifically points to the passages which describe the conservation of two structural motifs, one which interacts with the incoming dNPT, and contains a conserved sequence in almost all polymerases. Therefore, according to Applicant "In view of this reference, the Examiner's concerns regarding the number and kind of polymerases as claimed vis a vis enablement is completely alleviated." Applicant further argues that while Barnes teaches that a change in 10 or 13 amino acids can make a difference between thermostable or non-thermostable enzyme, Applicant is not engineering a thermostable enzyme, but one with longer read lengths. Applicant concludes with the following:

"As a class of enzymes, more mutations are performed on polymerases than probably any other enzyme class. Scores of scholarly articles, journal references and texts have been written on the subject. In fact, a great deal of practical guidance is in the art on the methodologies to achieve mutation and retain activity. Given the flexibility in achieving a functional polymerase with an attachment complex, Applicant submits that many mutations can be made in any polymerase, wherein anchors are engineered and if necessary, used to immobilize the enzyme."

However, as indicated by Barnes et al., even a simple change, like a deletion from either an N- or C-terminus can entirely change the properties of the resulting polymerase. Further, the same Patel et al. reference, which, by the way, has a title "DNA polymerase active site is highly mutable: Evolutionary consequences", states the following (Abstract):

"DNA polymerases contain active sites that are structurally super-imposable and highly conserved in sequence. To assess the significance of this preservation and to determine the mutational burden that active sites can tolerate, we randomly mutated a stretch of 13 amino acids within the polymerase catalytic site (motif A) of *Thermus aquaticus* DNA polymerase I. After selection, by using genetic complementation, we obtained a library of approximately 8,000 active mutant DNA polymerases, of which 350 were sequenced and analyzed. This is the largest collection of physiologically active polymerase mutants. We find that all residues of motif A, except one (Asp-610), are mutable while preserving wild-type activity. A wide variety of amino acid substitutions were obtained at sites that are evolutionarily maintained, and conservative substitutions predominate at regions that stabilize tertiary structures. Several mutants exhibit unique properties, including DNA polymerase activity higher than the wild-type enzyme or the ability to incorporate ribonucleotide analogs."

Therefore, it is clear from this passage that screening just 13 amino acids of a polymerase with 800 amino acids involves a very large amount of work. As stated by Patel et al. on page 5096, last paragraph, the mutagenic protocol was designed to substitute all of the 13 residues with all 19 of the other, therefore the potential number of different polymerases is 13^{19}, or 1.5×10^{20} different polymerases. Out of that number, 200,000 clones were obtained, and 8000 clones were recovered containing different polymerase sequences. Therefore the fraction of recovered clones was 5×10^{-17}

of the total possible clones. Further, as shown below by the summary of Patel et al. (page 5097, second and third paragraph), the results on polymerase activity varied with the number and type of substitution, therefore were completely unpredictable:

"To establish the spectrum of mutations that restored growth of *E. coli recA 718 polA12,* we sequenced the randomized insert from both unselected clones (30°C) and from selected clones (37°C). Analysis of sequences (Fig. 2A) from unselected plasmids, which reflects the distribution of mutants found in the random library before selection, shows that the average number of amino acid substitutions is four. In addition, several clones contained insertions, deletions, and stuffer fragments that arose during library construction. After selection, we randomly picked 350 colonies that grew at 37°C, measured *Taq* DNA polymerase activity, isolated the plasmids, and sequenced 200 nt encompassing the substituted random sequence. Of the 350 clones, 20 were inactive (2% DNA polymerase activity relative to WT); 39 clones had low activity at 72°C (2 to 10%); whereas 291 were active (>10 to 200% WT activity). The 291 independent active clones had on average two amino acid changes, ranging from none (27 clones) to 1 clone containing six amino acid changes; no selected active clone contained insertions or deletions (Fig. 2B).

A large number of these selected mutants retain DNA polymerase activity comparable to WT (66-200% WT). Of the 264 active mutants, approximately one-third of the mutants exhibit WT DNA polymerase activity (Fig. 2C). Most mutants containing a single amino acid substitution possess WT activity. Twenty percent (7 of 33) of mutants with four amino acid changes maintain normal activity, and a clone containing six amino acid substitutions also exhibits WT activity. The number of mutants exhibiting moderate activity (33-66% WT) or low activity (10-33% WT) follows a Poisson distribution relative to number of amino acid changes, with a median of two or three

amino acid substitutions per clone, respectively. Plasmids (27 clones) that encode WT enzyme at the amino acid sequence contain silent nucleotide substitutions; these enzymes have activities similar to those of WT controls. These data indicate that, even in cases of especially pronounced mutation burden with many amino acids substituted within an evolutionarily conserved motif, a large number of mutants can exhibit high activity."

Finally, as to the type of substitutions tolerated by the different amino acids in the active site, Patel et al. state (page 5097, fourth paragraph):

"Nature of Allowable Substitutions. Sequence analysis of all 291 selected active clones (10-200% WT activity; Fig. 3A), including the 87 most active clones (>66-200% WT activity; Fig. 3B), showed that most motif A residues tolerate a wide spectrum of substitutions (Leu-605, Leu-606, Val-607, Ala-608, Leu-609, Ser-612, Ile-614, and Arg-617), some residues tolerate predominantly conservative substitutions (Tyr-611, Gln-613, Glu-615, and Leu-616), and only one residue is immutable (Asp-610). Of the highly mutable residues, Ser-612, which is present in nearly all eukaryotic and prokaryotic DNA polymerases sequenced, tolerates substitutions that are diverse in size and hydrophilicity while often preserving WT-like activity. Consistent with these mutability data, structural analysis shows that Ser-612 projects away from the catalytic site and does not appear to maintain significant interactions. Of the other highly mutable amino acids, hydrophobic residues Leu-605 to Leu-609 form a strand of the structurally conserved antiparallel β sheet that accommodates the triphosphate portion of the incoming dNTP. That these hydrophobic residues can be replaced indicates none are essential for WT activity; in fact, a mutant with six substitutions (Leu-605 -> Arg, Leu-606 -> Met, Val-607 -> Lys, Ala-608 -> Ser, Leu-609 -> Ile, and Ser-612 -> Arg) exhibits WT DNA polymerase activity."

None of these resulted could be predicted from either the known structures of DNA polymerases or from the fact that the polymerase active site is highly conserved.

In view of the above, Patel et al. again reinforces the point that any changes to a sequence or structure of an enzyme are unpredictable, even in view of a large amount of data already accumulated in prior art.

The rejection is maintained.

Claim Interpretation

8. The term "attachment complex" has not been defined by Applicant, therefore it is considered as any molecule. Further, the term "polymerase has at least one anchor" is interpreted as "polymerase comprises at least one anchor" and the anchor is covalently attached to the polymerase. As there are no other requirements for the anchor, it is considered to be any molecule or a part of molecule, for example, a part of the polymerase.

9. In view of Applicant's amendment reciting "an attachment complex comprising said at least one anchor ", the structural limitations of claim 1 are interpreted as follows:

i) a polymerase,

ii) an anchor covalently attached to the polymerase,

iii) an attachment complex, which also comprises the anchor (therefore the anchor is shared by the polymerase and the attachment complex),

iv) nucleic acid "entrapped" by the anchor.

10. Applicants did not define the term "entrapped", therefore any association between the nucleic acid and anchor, direct or indirect, is considered to anticipate this limitation.

11. Applicant did not define the term "modified amino acid", therefore any modification, i.e., labeling, attachment of other amino acids, etc. is considered to anticipate this term.

12. Applicant did not define the term "irreversible association", therefore, any association is considered as irreversible, provided the time scale or topological constraints.

13. Applicant defined the term "processivity index" on page 7, [0038], as the number of nucleotides sequenced divided by the number of nucleotides in the template.

Claim Rejections - 35 USC § 112, new matter

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-3, 18, 19, 22, 23 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant amended claim 1 to introduce the following limitation:

"...wherein the other end of the anchor is i) attached to said polymerase, ii) to a topological tether or iii) to a support, wherein said anchor serves to entrap said target nucleic acid;".

Applicant indicates that support for this amendment is indicated on page 8, line 14, and in Figures 1B, C and D.

Page 8, lines 13-15, state as follows:

"In certain instances, the at least one anchor entraps the target nucleic acid such as by folding back on itself."

The claim limitations require that the anchor be covalently attached with one end to the polymerase, and with the other end either to a polymerase, to a topological tether or to a support. There is no option of the anchor folding back on itself to entrap the nucleic acid, which requires the other end of the anchor to be free.

Further, there is no support in the disclosure or in the originally filed claims for the limitation of both ends of the same anchor to be attached to the polymerase. Cited below is paragraph [0042] on page 8, lines 20-28), describing Figures 1B and 1C:

"As shown in FIG. 1B, an anchor 130 can further comprise other functionalities such as a first member 135 of a first binding pair. A second anchor 140 has a first member 145 of a second binding pair. As shown in FIG. 1C, in certain instances, a topological tether is formed when the first members 135, 145 are joined by a common member 148. Alternatively, a topological tether can be formed when the first members 135, 145 are each joined directly to a support (not shown). A topological tether and at least one anchor can attach via complementary binding pairs. Alternatively, the anchors can attach directly to a substrate without the use of a tether (for example, histidine patches as anchors bound directed to a Ni surface)." In Fig. 1C, there are two anchors bound to two different sites of the polymerase, joined to a first and second binding pairs, which, in turn, are joined to a common member.

Therefore the disclosure does not provide support for a limitation of an anchor joined with both ends to the polymerase to entrap the nucleic acids, thus this limitation constitutes new matter.

Claim Rejections - 35 USC § 112, written description

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-3, 18, 19, 22, 23 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of polymerases none of which are disclosed in the specification in terms of their structures, i.e., their amino acid sequences. The claimed genus encompasses all possible polymerases, i.e., DNA and RNA polymerases, with the only functional limitation that the polymerase has to have an "anchor", the structure of which is not defined, covalently attached. These claims further encompass alternately spliced versions of the proteins, allelic variants including insertions and mutations as well as proteins altered in their domain structure, and no specific amino acid sequences have been provided.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the polymerase having an attachment complex comprising an anchor lack any specific structure, and is precisely the situation of naming a type of material which is generally known to likely exist, but is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "a polymerase-nucleic acid complex comprising a polymerase having an attachment complex comprising an anchor", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a polymerase comprising an attachment complex, without any definition of the particular polymerase claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any polymerases as claimed. Therefore, the claims fail to meet the written description requirement by encompassing polymerases which are not described in the specification.

Claim Rejections - 35 USC § 112, enablement

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 1-3, 18, 19, 22, 23 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-3, 18, 19, 22, 23 and 26 are broadly drawn to a polymerase-nucleic acid complex, in which the polymerase comprises an attachment complex which comprises at least one anchor covalently attached to the polymerase. However, as will be further discussed, there is no support in the specification and prior art for the structure as claimed. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has no working examples of any polymerases comprising an attachment complex which irreversibly associates the polymerase with a target nucleic acid.

Guidance in the Specification.

The specification provides no evidence that the claimed polymerase can be produced as claimed. The only mention of any specific polymerase is in paragraph [0050] and [0051] on pages 11 and 12, where it mentions a Therminator polymerase (no specific amino acid sequence provided) which has two peptides attached to amino acid positions K53 and K229. No such polymerase was produced by Applicant and there is no evidence that it would function as claimed. Considering the large number of polymerases with differing structures and function, i.e., DNA- and RNA-dependent DNA polymerases and RNA- and DNA-dependent RNA polymerases, for example, the guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

The unpredictability of the art and the state of the prior art

There is a great deal of unpredictability in the modification of structural properties of polymerases, due to the diversity of their amino acid sequences and corresponding three-dimensional structures. As evidenced by Braithwaite et al. (Nucl. Acids Res., vol. 21, pp. 787-802, 1993), in 1993 there were three families of DNA polymerases (A, B and C) and about 56 known amino acid sequences (page 787, Fig. 1). As can be seen from Table 1 (page 800), the polymerases have different amino acid sequences and properties. Brautigam et al. (Curr. Opinion Struct. Biology, vol. 8, pp. 54-63, 1998) presented a review of known structures of DNA and RNA polymerases. Even though the polymerases in general share certain similarities of the polymerase domain, the details of the structures differ from polymerase to polymerase even within a single family (Fig. 2; page 58, fifth paragraph; page 62, last paragraph).

Therefore, since the structure of any given protein is influenced by all of its components, introduction of mutations or additional structural elements is by no means routine in terms of obtaining a functional protein. This is supported by evidence provided by Barnes (U.S. Patent No. 5,436,149 A), which discloses construction of a thermostable DNA polymerase which can remain functional above 97° C. The constructs involved deletions of amino acids 1-278, 1-288 and 1-291 of Thermus aquaticus DNA polymerase (col. 5, lines 60-68; col. 6, lines 1-55), and the best result was obtained with a polymerase which had residues 1-278 removed (Fig. 4, for example). Therefore, deletion of only additional 10 or 13 amino acids markedly changed the thermostability properties of the enzyme. As stated by Barnes (col. 1, lines 67 and 68; col. 2, lines 1-17):

"The development of other enzymatically active mutein derivatives of Thermus aquaticus DNA polymerase is hampered, however, by the unpredictability of the impact of any particular modification on the structural and functional characteristics of the protein. Many factors, including potential disruption of critical bonding and folding patterns, must be considered in modifying an

enzyme and the DNA for its expression. A significant problem associated with the creation of N-terminal deletion muteins of high-temperature Thermus aquaticus DNA polymerase is the prospect that the amino-terminus of the new protein may become wildly disordered in the higher temperature ranges, causing unfavorable interactions with the catalytic domain(s) of the protein, and resulting in denaturation."

In conclusion, any modification of a protein structure requires extensive testing to verify that the desired properties are obtained and that the protein retains its function.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to produce claimed polymerases, including selection of possible anchoring sites for each of the polymerases, different types of anchors (peptides, nucleic acids, etc), influence of the modification on the protein structure and processivity, influence of reaction conditions (pH, temperature, type of nucleotides used). This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the structure and properties of a modified polymerase depend upon numerous known and unknown parameters such as the influence of each residue on the protein stability and function, potential tertiary structure

changes affecting function under certain reaction conditions, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

21. Claims 1-3, 18 and 26 are rejected under 35 U.S.C. 102(a) as being anticipated by Motz et al. (J. Biol. Chem., vol. 277, pp. 16179-16188, May 2002; cited in the IDS and in the previous office action).

Regarding claims 1 and 26, Motz et al. teach a Taq polymerase-nucleic acid complex, where the polymerase comprises a PCNA-binding domain (= anchor) covalently attached to the polymerase and PCNA (= topological tether) assembled on the binding domain (PCNA-binding domain +PCNA =attachment complex), which irreversibly associates the polymerase with the nucleic acid with the nucleic acid during the replication phase to increase processivity (Abstract; page 16180, second paragraph; page 16181, third and last paragraphs; page 16183, second paragraph; page 16186, second and third paragraphs; Fig. 4). Motz et al. teach a Taq DNA

polymerase with a PCNA binding motif (=an anchor), which is modified at its N-terminus by the presence of a six amino acid linker and 42 amino acid polB C-terminal amino acids (Fig. 4A).

Regarding claim 2, Motz et al. teach primers for the target nucleic acid (page 16181; third paragraph).

Regarding claim 3, Motz et al. teach a six amino acid linker and the PCNA-binding domain, therefore they teach two anchors (page 16183, second paragraph).

Regarding claim 18, Motz et al. teach circular DNA (page 16181; third paragraph).

Claim Rejections - 35 USC § 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. Claims 19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motz et al. (J. Biol. Chem., vol. 277, pp. 16179-16188, May 2002; cited in the IDS and in the previous office action) and Blanco et al. (U.S. Patent No. 5,198,543 A; cited in the previous office action).

A) Motz et al. teach Taq DNA polymerase, but do not teach strand displacement synthesis or polymerases of claim 22.

B) Blanco et al. teach using phi29 DNA polymerase for strand displacement amplification and sequencing (col. 1, lines 9, 10; col. 2, lines 3-35; col. 4, lines 18-52; col. 8, lines 46-51 and 54-57).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the phi29 DNA polymerase of Blanco et al. as a polymerase of Motz et al. Blanco et al. specifically teach that phi29 polymerase can be used in place pf a Taq polymerase (col.

8, lines 54-57). The motivation to do so, provided by Blanco et al., would have been that the polymerase did not require temperature cycling and produced long strands of DNA (col. 8, lines 46-51).

24. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Williams (U.S. Patent No. 6,255,083 B1; cited in the previous office action) and Motz et al. (J. Biol. Chem., vol. 277, pp. 16179-16188, May 2002; cited in the IDS and in the previous office action).

A) Regarding claim 23, Williams teaches sequencing of nucleic acids using DNA polymerases immobilized on solid supports and Klenow DNA polymerase (col. 2, lines 16-36; col. 14, lines 21-58) as well as Taq polymerase (col. 17, lines 43-58). Williams does not teach irreversible association of the polymerase with nucleic acid target.

B) Motz et al. teach a Taq polymerase-nucleic acid complex, where the polymerase comprises a PCNA-binding domain (= anchor) covalently attached to the polymerase and PCNA assembled on the binding domain (=attachment complex), which irreversibly associates the polymerase with the nucleic acid with the nucleic acid during the replication phase to increase processivity (Abstract; page 16180, second paragraph; page 16181, third and last paragraphs; page 16183, second paragraph; page 16186, second and third paragraphs; Fig. 4). Motz et al. teach a Taq DNA polymerase with a PCNA binding motif (=an anchor), which is modified at its N-terminus by the presence of a six amino acid linker and 42 amino acid polB C-terminal amino acids (Fig. 4A).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the modified Taq polymerase of Motz et al. in the nucleic acid sequencing method of Williams. The motivation to do so, provided by Motz et al., would have been that the modification increased the Taq polymerase processivity (page 16186, second paragraph; Fig. 4).

25. No claims are allowed.

Conclusion

26. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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